A prospective clinical trial for assessing the efficacy of a minimally invasive protocol in patients with bisphosphonate-associated osteonecrosis of the jaws

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Objective. The objective of this study was to assess whether a minimally invasive protocol can be effective in the long-term control of necrotic areas and pain in patients suffering osteonecrosis of the jaw associated with the use of bisphosphonate drugs (BRONJ).
Study design. Thirty-four consecutive patients (14 male, 20 female) with BRONJ under treatment with zoledronate, pamidronate, or alendronate were enrolled. All of the patients received professional oral hygiene treatment and antiseptic oral rinses, and if in pain they assumed an antibiotic therapy with amoxicillin/clavulanate potassium and metronidazole for ten days. At the baseline visit, as well as at each 3-month recall, the size of the osteonecrotic lesions were measured and the pain level assessed with a visual analog scale.
Results. The results from the general linear model showed a statistically significant ($F = 16.1$; $P < .01$; $r^2 = 0.95$) time-related decrease in the size of exposed bone areas during the nonsurgical therapy (from 12.5 ± 12.0 mm to 8.8 ± 10.3 mm).
Conclusions. This conservative protocol seems to provide successful treatment in the vast majority of patients. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:777-782)**

In 2003, several cases of osteonecrosis of the jaw (ONJ) were reported in patients receiving bisphosphonate therapy.[1-3] Since then, the number of reported cases has increased, and the literature now includes several hundred cases. The disorder has been defined as "a condition characterised by exposure of bone in the mandible or maxilla persisting for more than eight weeks in a patient who has taken or currently is taking a bisphosphonate and who has no history of radiation therapy to the jaws. Clinically, the disease presents as exposed alveolar bone that occurs spontaneously or becomes evident following an invasive surgical procedure such as tooth removal, periodontal surgery, apicoectomy, or dental implant placement."[4,5]

Bisphosphonate-associated ONJ is characterized by a local alteration of the osteoclast/osteoblast axis, with a relative decrease in osteoclast activity and local inhibition of angiogenesis.[6,7] Once an area of bone necrosis is produced by trauma, periodontal or periradicular disease, or any dental procedure, osteoclasts cannot activate or aggregate sufficiently to remove the necrotic bone. When the volume of necrotic bone reaches a sufficient size, it may produce local changes that impair local bony, vascular, and connective tissue structures necessary for self-repair. Because the oral cavity is never aseptic, superimposed bacterial cofactors inevitably produce sequestration, which may lead to osteomyelitis and prevent or inhibit epithelial regeneration over the exposed bone. In addition, zoledronic acid itself, which has a dose-dependent effect on apoptosis and cell proliferation, may affect fibroblast and epithelial cells.[6] Bisphosphonate-associated ONJ usually appears as areas of necrotic exposed bone surrounded by inflamed gingiva or mucosa[8]; it usually has a significant adverse effect on the quality of life for most patients.[9-11]

To date, several recommendations have been proposed for treating ONJ, but no consensus on a standard of care has been reached, nor is there any agreement on a surgical versus nonsurgical approach to therapy.[11-14] This probably results from the lack of reported randomized clinical trials comparing different management strategies designed to allow the area of exposed bone to recover. Such clinical trials entail objective difficulties to a scientific approach, i.e., randomizing groups of oncology patients whose quality of life is strictly related to these drugs.

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Our previous study evaluated the efficacy of 2 different procedures for treating patients with ONJ and adopted an objective parameter to quantify the efficacy of each protocol.[14] The preliminary results did not show any significant difference between surgical and nonsurgical approaches and suggested that an antibiotic regimen was effective in the short-term management of these patients.

In the present study, we enrolled a larger group of patients and followed them prospectively for a longer period of time, with the aim of assessing whether a minimally invasive protocol is effective in the long-term control of necrotic areas and pain.

MATERIALS AND METHODS

This prospective study enrolled 34 consecutive patients with ONJ (14 male, 20 female, mean age 69.0 ± 7.1 years, range 48-85 years) who presented to the Department of Oral Science of the University of Bologna School of Dentistry during the past 3.5 years. Twenty-seven patients had been treated with zoledronate, 3 with pamidronate, and 4 with alendronate. No patient had evidence of maxillary or mandibular metastasis or a history of radiation therapy. Twelve patients had multiple myeloma, 11 had metastatic breast carcinoma, 6 had metastatic prostate carcinoma, 3 had a history of osteoporosis, and 1 each had metastatic kidney carcinoma and paraganglioma.

The median time from the beginning of bisphosphonate treatment to the diagnosis of osteonecrosis was 39 months (range 8-180 months). Necrotic bone developed after a dental extraction in 21 patients, and it appeared spontaneously in 12 patients and after professional oral hygiene treatment in 1 patient. The location was the mandible in 25 patients and the maxilla in 9. No patient discontinued the bisphosphonate therapy after the diagnosis of ONJ.

At the first examination, the maximum diameter of the area of exposed bone was carefully measured in millimeters using a probe and was recorded by an external observer. The patient's pain was self-evaluated using a visual analog scale (VAS).

All patients received professional oral hygiene treatment and oral hygiene instructions that recommended antiseptic oral rinses twice a day, switching between chlorhexidine digluconate 0.12% (Corsodyl; GlaxoSmithKline, Brentford, Middlesex, U.K.) and essential oils (Listerine; Johnson and Johnson, New Brunswick, NJ, USA) every 2 weeks to avoid bacterial resistance.

All patients were followed carefully every 3 months. At each recall visit, the maximum diameter of the exposed area was measured carefully and recorded by an external observer, and the pain was reevaluated using the VAS. Any area of necrotic bone that was mobile was removed gently with tissue pliers, and the rough surface of the bone was smoothed using piezosurgery tips (P10 insert, Piezosurgery; Mectron, Genova, Italy). During each visit, the operator also evaluated mucosal surfaces, periodontal probing, thermic tooth vitality, halitosis, and tissue swelling. Prosthetic devices were controlled and, if necessary, modified to remove traumatic triggers on the tissues.

All patients who were in pain and/or showed purulent drainage received an antibiotic therapy consisting of amoxicillin/clavulanate potassium as 1-g tablets every 8 hours for the first 2 days and every 12 hours for the next 8 days, and metronidazole 500 mg (2 × 250-mg tablets) every 12 hours for 10 days. Alternatively, if a patient was allergic to penicillin, the antibiotic therapy consisted of ciprofloxacin 500 mg every 12 hours for 10 days, and metronidazole 500 mg (2 × 250-mg tablets) every 12 hours for 10 days. The antibiotic therapy was repeated only when pain was present or reported during the follow-up visits.

This protocol was authorized by the Independent Ethics Commitee of S. Orsola Hospital.

One patient (a 65-year-old woman treated with zoledronate for metastatic breast carcinoma) died during the follow-up period and was removed from the study.

Statistical analysis

One-way analysis of variance (ANOVA) was used to determine any significant differences in the initial area of exposed bone and the location of the necrotic areas (mandible or maxilla), type of bisphosphonate therapy, and gender.

A linear model was fitted to evaluate the relationships between age and the duration of bisphosphonate therapy and area of exposed bone. After fitting a general linear model, a multiple regression (ANOVA) for repeated measures was applied to identify any significant time-associated difference in the maximum diameter of exposed bone, with the location of the exposed bone (mandible or maxilla), initial size of the exposed area, and type and duration of bisphosphonate therapy included in the general linear model as confounding variables.

RESULTS

The mean follow-up duration was 16.0 ± 9.4 months (range 3-40 months).

Table I presents the clinical findings for the entire patient population before and after the proposed minimally invasive protocol.

The 1-way ANOVA did not reveal any statistical difference in the initial extent of exposed bone between the mandible (13.2 ± 12.9 mm) and maxilla (10.4 ± 9.5), between men (12.7 ± 10.5 mm) and women (12.3 ± 13.2